Complete Summary

GUIDELINE TITLE

Practice parameters for anal squamous neoplasms.

BIBLIOGRAPHIC SOURCE(S)

Fleshner PR, Chalasani S, Chang GJ, Levien DH, Hyman NH, Buie WD, Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for anal squamous neoplasms. Dis Colon Rectum 2008 Jan;51(1):2-9. [82 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Anal squamous neoplasms, including:

- Anal canal squamous cell carcinoma
- Anal margin squamous cell carcinoma
- Anal intraepithelial neoplasia (AIN)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management

Risk Assessment
Treatment

CLINICAL SPECIALTY

Colon and Rectal Surgery
Oncology
Radiation Oncology

INTENDED USERS

Health Care Providers
Patients
Physicians

GUIDELINE OBJECTIVE(S)

To provide practice parameters for the evaluation and treatment of anal squamous neoplasms

TARGET POPULATION

Adults with anal squamous neoplasms

INTERVENTIONS AND PRACTICES CONSIDERED

Anal Canal Squamous-Cell Carcinoma

Evaluation

1. Disease-specific history and physical examination, including assessment of risk factors, comorbidities, and digital rectal examination (DRE)
2. American Joint Commission on Cancer/International Union against Cancer (AJCC/UICC) staging, including palpation, fine-needle aspiration, or core biopsy of lymph nodes
3. Endoscopic and radiologic evaluations (anoscopy, sigmoidoscopy, colonoscopy, endoanal ultrasound [ERUS], computed tomography [CT], positron emission tomography [PET])
4. Histology of mass
5. CD4 counts for patients with human immunodeficiency virus (HIV)

Treatment

1. Combined chemoradiation therapy (CRT) with 5-fluorouracil (5-FU)
2. Multidrug CRT (5-FU plus mitomycin C)
3. Radiation alone in selected cases
4. Higher dose radiation in selected cases
5. Abdominoperineal resection for persistent of recurrent disease
6. Systemic chemotherapy for extrapelvic metastasis or recurrence after surgery
7. Highly active antiretroviral therapy (HAART) plus CRT for patients with HIV
8. Posttreatment surveillance/follow-up

Anal Margin Squamous-Cell Carcinoma

1. Evaluation as above
2. Tumor staging as for skin cancer
3. Wide local excision for T1/T2 tumors
4. CRT with 5-FU plus mitomycin C or cisplatin for T3/T4 lesions
5. Abdominoperineal resection in selected cases

Anal Intraepithelial Neoplasia (AIN)

Evaluation

1. Disease-specific history, physical examination, and risk assessment
2. Anal Papanicolaou smear cytologic examination

Treatment

1. Observation alone
2. Topical 5 percent imiquimod cream
3. Topical 5 percent 5-FU cream
4. Photodynamic therapy
5. Targeted destruction by surgical ablation or infrared coagulation (IRC)and close clinical follow-up
6. Follow-up

MAJOR OUTCOMES CONSIDERED

- Response rate
- Local control rate
- Recurrence rate
- Overall survival
- Disease-free survival
- Colostomy-free survival
- Side effects
- Specificity and sensitivity of diagnostic tests

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A MEDLINE search of English language references from 1965 through December 2006 was performed by using the following key words: "anal cancer"; "anal carcinoma"; "anal intraepithelial neoplasia"; and "squamous-cell cancer." The Cochrane Database of Collected Reviews and selected embedded references also were reviewed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

I. Meta-analysis of multiple well-designed, controlled studies, randomized trials with low false-positive and low false-negative errors (high power)
II. At least one well-designed experimental study; randomized trials with high false-positive or high false-negative errors or both (low power)
III. Well-designed, quasi-experimental studies, such as nonrandomized, controlled, single-group, preoperative-postoperative comparison, cohort, time, or matched case-control series
IV. Well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V. Case reports and clinical examples

Adapted from Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1992;102(4 Suppl):305S–11S. Sacker DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;92(2 Suppl):2S–4S.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendations

A. Evidence of Type I or consistent findings from multiple studies of Type II, III, or IV
B. Evidence of Type II, III, or IV and generally consistent findings
C. Evidence of Type II, III, or IV but inconsistent findings
D. Little or no systematic empirical evidence

Adapted from Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1992;102(4 Suppl):305S–11S. Sacker DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;92(2 Suppl):2S–4S.

COST ANALYSIS

Although some economic modeling studies have suggested that frequent anal cytology may be a cost-effective method to prevent anal cancer, there have not been any randomized or cohort studies to demonstrate improved survival or outcomes.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (**I-V**) and the grades of recommendations (**A-D**) are defined at the end of the "Major Recommendations" field.

Anal Canal Squamous-Cell Carcinoma

Pretreatment Evaluation

A. A disease-specific history should be taken, emphasizing symptoms and predisposing factors. **Level of Evidence: IV; Grade of Recommendation: B.**

   Most patients with anal squamous cell carcinoma (SCC) have anal bleeding (which frequently can be mistaken for hemorrhoidal bleeding), pain, or the sensation of a mass; however, 20 percent of patients are asymptomatic. Groin pain may indicate inguinal lymph node involvement. Risk factors that have been associated with carcinoma of the anus include infection with the human papillomavirus (HPV) or human immunodeficiency virus (HIV), a history of cervical cancer, cervical intraepithelial neoplasia, other sexually acquired diseases, cigarette smoking, anoreceptive intercourse, multiple sexual partners, and immunosuppression. A history of medical comorbidities that might limit the patient's ability to undergo chemoradiation or radical surgery also should be sought.

B. A disease-specific physical examination should be performed to determine tumor size and possible lymph node involvement. **Level of Evidence: IV; Grade of Recommendation: B.**

Fixation and location of the tumor within the anal canal also should be determined to aid in subsequent treatment and evaluation. Perirectal lymph nodes may sometimes be palpated on digital rectal examination. The presence or absence of inguinal adenopathy should be ascertained by palpation. A fine-needle aspiration or core biopsy of an enlarged inguinal lymph node with or without ultrasound guidance may supplement the physical examination and confirm malignant involvement.

C. Endoscopic and radiologic evaluation should be performed. **Level of Evidence: IV; Grade of Recommendation: B.**

Biopsy via anoscopy or sigmoidoscopy allows histologic confirmation that a suspicious mass within the anal canal is a primary anal epidermoid cancer (squamous-cell) and not a primary rectal cancer (adenocarcinoma) or anal glandular adenocarcinoma. Patients older than aged 50 years or those with risk factors for concomitant colorectal cancer, such as hematochezia, alterations in their bowel habits, or predisposing family history, should undergo colonoscopy to rule out a synchronous colorectal neoplasm.

Endoanal ultrasound (ERUS) may be useful and has been reported to be superior to physical examination in assessing tumor involvement of the anal sphincter and perirectal lymph nodes. Computed tomography (CT) scans should usually be performed in the pretreatment evaluation of anal cancer to exclude metastatic disease. Positron emission tomography (PET) scanning may have a role as an adjunct to CT of the pelvis, abdomen, and chest, identifying sites of metastasis not observed on CT in 25 percent of cases. Almost 20 percent of patients with inguinal nodes that are negative by both physical examination and CT scan are positive on PET. This has prognostic significance and may influence the radiation treatment plan.

Treatment

A. *Primary Treatment*
   1. Combined modality chemoradiation therapy should usually be first-line therapy: **Level of Evidence: I; Grade of Recommendation: A.**

      Since the first description by Nigro of complete pathologic responses to concurrent 5-fluorouracil (5-FU), mitomycin C, and radiation therapy in patients with anal cancer, further study has established primary chemoradiation (CRT) therapy as the first-line treatment for squamous-cell carcinoma of the anal canal.

      Radiation therapy (RT) alone may be considered in patients who cannot tolerate the additional toxicity of chemotherapy. Local excision is an appropriate consideration for small, superficial lesions.

   2. Multidrug chemotherapy with radiation is usually preferable to single drug chemotherapy with radiation: **Level of Evidence: I; Grade of Recommendation: A.**
   3. Higher doses of radiation therapy without prolonged breaks in treatment is preferable when tolerated: **Level of Evidence: III; Grade of Recommendation: B.**

B. *Treatment of Recurrent or Persistent Disease*

1. Abdominoperineal resection is effective salvage therapy for persistent or recurrent disease: **Level of Evidence: III; Grade of Recommendation: B.**

   Abdominoperineal resection (APR) is primarily reserved for salvage therapy when CRT has failed to achieve a complete response or when a local recurrence is diagnosed. APR also may be considered in patients with severe radiation therapy-induced complications, including stenosis, nonhealing ulceration, or incontinence.

2. Systemic chemotherapy should be considered in patients with extrapelvic metastasis or recurrence after surgical salvage: **Level of Evidence: III; Grade of Recommendation: B.**

C. *Management of Inguinal Lymph Node Disease*

1. Chemoradiation is the treatment of choice for inguinal lymph node disease: **Level of Evidence: III; Grade of Recommendation: B.**

   CRT is the treatment of choice for synchronous nodal involvement, with cure rates approaching 90 percent. Both inguinal nodal basins should be incorporated into the radiation fields with the addition of a boost technique for clinically positive lymph nodes. Metachronous lymph nodes are seen in 10 to 20 percent of patients, usually appearing within six months after treatment of the primary lesion. These lymph node deposits also respond well to CRT. Lymph node dissection may be considered in patients who have persistent nodal disease after CRT.

   Prophylactic lymph node dissection is not indicated because of the potential for serious long-term wound and lower extremity complications. Sentinel lymph node dissection is an appealing concept for detecting occult metastasis to the inguinal nodes. Nevertheless, the clinical impact of this procedure on the therapeutic approach is unclear as long as the inguinal nodes are included in the radiation field.

D. *Anal Cancer in HIV-Positive Patients*

1. CD4 counts may be used to predict the outcome and tolerance of CRT in HIV-positive patients: **Level of Evidence: III; Grade of Recommendation: B.**

   Patients with CD4 counts >200 cells/mL should usually be treated with combined chemoradiation as with non-HIV infected individuals. Patients with CD4 <200 cells/mL tend to experience more toxicity from CRT and therapy must be individualized in this setting. Highly active antiretroviral therapy (HAART) allows patients to better tolerate CRT and may improve local tumor control.

Posttreatment Surveillance

1. Follow-up should usually include digital rectal examination, anoscopy, and inguinal palpation. **Level of Evidence: IV; Grade of Recommendation: B.**

   Patients should be followed since recurrences often may be retreated for cure. Examinations may be performed every three to six months with digital rectal examination, anoscopy with biopsy of any suspicious lesion, inguinal palpation, and perhaps CT scan for more advanced disease.

Anal Margin Squamous Cell Carcinoma

A. A disease-specific physical examination should be performed, emphasizing tumor size and anatomic location. **Level of Evidence: IV; Grade of Recommendation: C.**

   Significant differences in treatment and survival distinguish anal margin cancers from anal canal tumors; the location of these tumors must be accurately assessed.

   Wide local excision alone is appropriate for T1 and early T2 lesions that can be excised with a 1-cm margin. However, larger cancers usually should be treated with the addition of prophylactic radiation to the inguinal lymph nodes along with radiation or excision of the primary tumor. For T3 and T4 lesions, radiation to both inguinal regions and the pelvis, along with chemotherapy, such as 5-fluorouracil and mitomycin C or cisplatin, usually should be added. APR is most appropriate for patients who are already incontinent with large, bulky tumors extending into the sphincter muscle or in patients who have failed CRT.

Anal Intraepithelial Neoplasia (AIN)

Pretreatment Evaluation

A. A disease-specific history should be taken, emphasizing symptoms and predisposing factors. **Level of Evidence: IV; Grade of Recommendation: B.**

   AIN is being detected with increasing frequency in both males and females with impaired immune function. HIV seropositivity is not only an established risk factor for AIN but it also is associated with progression to high-grade anal squamous intraepithelial lesion (HSIL), particularly in patients with a low CD4 cell count. AIN also is associated with immunosuppression for organ transplantation.

   The association between HPV infection and AIN has been demonstrated in both males and females.

B. Anal Papanicolaou smear cytological examination may be useful in the detection and follow-up of AIN. **Level of Evidence III; Grade of Recommendation: C.**

Based on numerous similarities between AIN and cervical intraepithelial neoplasia (CIN), anal Papanicolaou (Pap) smear cytology has been proposed for both screening of high-risk individuals and surveillance after treatment of AIN.

Treatment

A. Observation alone with close clinical follow-up is an appropriate management option for AIN. **Level of Evidence: IV; Grade of Recommendation: C.**

   Excision is reserved for clinically definable lesions.

   There is no need for an aggressive search for visceral malignancy.

B. Topical 5 percent imiquimod cream is appropriate therapy for AIN. **Level of Evidence: IV; Grade of Recommendation: C.**
C. Topical 5 percent 5-fluorouracil cream is an appropriate treatment option for AIN. **Level of Evidence: IV; Grade of Recommendation: C.**
D. Photodynamic therapy is an appropriate treatment option for AIN. **Level of Evidence: V; Grade of Recommendation: D.**
E. Targeted destruction and close clinical follow-up is appropriate therapy for AIN. **Level of Evidence: III; Grade of Recommendation: C.**

   Targeted destruction guided by high-resolution anoscopic examination is effective to identify, biopsy, and destroy high-grade AIN without the morbidity associated with wide local excision, but there is a high risk for persistent or recurrent disease among HIV-positive patients.

   Infrared coagulation (IRC) also has been used as an effective ablative device and may be associated with less pain; nevertheless, IRC also has been associated with a high risk of recurrence among HIV-positive males.

F. Patients with AIN should be offered follow-up. **Level of Evidence: III; Grade of Recommendation: B.**

   Patients with AIN should usually be monitored for the development of anal cancer. Surveillance examinations may be performed at six-month intervals as long as dysplasia is present. This approach allows for retreatment of recurrent or persistent dysplasia or for the detection of invasive squamous cell carcinoma. Follow-up generally includes anoscopic examination, with or without the aid of magnification or the application of acetic acid and Lugol's solution. The importance of close follow-up should be particularly emphasized among HIV-positive patients who have been shown to have a high risk of persistence or recurrence of high-grade dysplasia, regardless of primary treatment modality.

Definitions:

Levels of Evidence

I. Meta-analysis of multiple well-designed, controlled studies, randomized trials with low false-positive and low false-negative errors (high power)
II. At least one well-designed experimental study; randomized trials with high false-positive or high false-negative errors or both (low power)
III. Well-designed, quasi-experimental studies, such as nonrandomized, controlled, single-group, preoperative-postoperative comparison, cohort, time, or matched case-control series
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C. Evidence of Type II, III, or IV but inconsistent findings
D. Little or no systematic empirical evidence

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Lower rates of local failure or tumor recurrence
- Reduced need for colostomy
- Higher rates of disease-free and overall survival
- Early detection of recurrent anal squamous neoplasia

POTENTIAL HARMS

- Hematologic toxicity, complications and need for colostomy with chemoradiation therapy (CRT)
- Perineal wound morbidity after salvage abdominoperineal resection (APR)
- Local side effects, including irritation, burning, and erosions, which adversely affect patient compliance from topical creams
- High rates of disease recurrence and anal incontinence or stenosis with wide excisional therapy of anal intraepithelial neoplasia (AIN)

Special Population

Human immunodeficiency virus (HIV) patients with CD4 counts <200 cells/ml tend to experience more toxicity from chemoradiation (CRT).

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These guidelines are inclusive, and not prescriptive. Their purpose is to provide information on which decisions can be made, rather than dictate a specific form of treatment.
- It should be recognized that these guidelines should not be deemed inclusive of all proper methods of care or exclusive of methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician in light of all of the circumstances presented by the individual patient.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Fleshner PR, Chalasani S, Chang GJ, Levien DH, Hyman NH, Buie WD, Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for anal squamous neoplasms. Dis Colon Rectum 2008 Jan;51(1):2-9. [82 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Jan

GUIDELINE DEVELOPER(S)

American Society of Colon and Rectal Surgeons - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Colon and Rectal Surgeons

GUIDELINE COMMITTEE

Standards Practice Task Force of The American Society of Colon and Rectal Surgeons

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Society of Colon and Rectal Surgeons Web site.

Print copies: Available from the ASCRS, 85 W. Algonquin Road, Suite 550, Arlington Heights, Illinois 60005.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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